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## Setting Cleaning Validation Acceptance Limits for Topical Formulations

By M. Ovais, Lai Yeo Lian

*There is a need for current cleaning validation methods to be used for topical formulations. The authors highlight the issues and challenges encountered.*

Pharmaceutical manufacturing requires the selection of residue acceptance levels for potential residues such as active pharmaceutical ingredients (APIs), excipients, degradation products, cleaning agents, bioburden substances, and endotoxins when carrying out cleaning validation studies. These levels are determined according to the potential pharmacological, safety, toxicity, stability, and contamination effects on the next product produced with the same surface or equipment. The US Food and Drug Administration's guidance for determining residue limits states that residue limits should be logical, practical, achievable, and verifiable (1). Limits are typically set for visual, chemical, and microbiological residues by taking into consideration the batch size, dosing, toxicology, and surface area for the equipment.

In contrast to solid and liquid formulations, topical semi-solid formulations such as creams and ointments pose far more difficulty in cleaning because they contain greasy ingredients such as waxes and oils. These ingredients may inhibit wetting by cleaning agents, thereby limiting the ability to clean-rinse the residual product away.

Topical formulations (TFs) generally are considered to be safe and less potent than oral or injectable formulations. Nonetheless, the APIs and excipients commonly used in TFs may produce significant adverse effects in the form of skin irritation, skin sensitization, hypersensitivity, and photosensitivity reactions. Therefore, one must determine the carryover of residues from one product to another in a scientifically justified manner to limit the chances of adverse reactions and possibility of synergistic pharmacological effects between products and their ingredients.

The available guidelines and literature on cleaning validation provide possible approaches for setting the residual acceptance levels for APIs and finished products but contain little or no guidance regarding the ways to use these approaches for TFs (2–5). Although the existing approaches are more logical and appropriate for generating residual acceptance levels for solid and liquid formulations, they can also be applied to TFs with logical modifications. This article discusses the possible ways to set the residual acceptance levels for APIs present in TFs as a prerequisite for conducting cleaning validation studies.

### Background

The method widely used within the pharmaceutical industry for setting residual acceptance levels is the one provided by Fourman and Mullen, whose paper is listed in the reference section of the FDA cleaning validation guidance document (2). The method is based on the following criteria:

- The dose criterion is based on the principle that an API should not be present in a subsequently produced product at levels higher than 1/1000 of the minimum daily dose of the API in a maximum daily dose of the subsequent product.
- The 10-ppm criterion is based on the principle that any API should not be present in a subsequently produced product at levels higher than 10 ppm.
- The visually clean criterion states that the equipment should have a fixed value of no higher than 100 µg per 2 × 2 in. swab area.

This article uses the same principles to generate cleaning validation residue acceptance levels for TFs.

### Criterion based on product strength

One basis for establishing limits is a mathematical calculation that allows a certain fraction of the therapeutic dose to carry over into the maximum daily dose of the following product. The dose fraction allowed to carry over is referred to as maximum allowable carryover (MACO) and is based on the acceptable daily intake (ADI) of the API being cleaned. Industry uses various approaches to determine the ADI values for active ingredients and involve using minimum recommended therapeutic daily dose, lowest marketed dose, or no observable effect level (NOEL)/LD50 (lethal dose 50%) values divided by a safety factor (5). Some manufacturers use an occupational exposure limit (OEL) value to calculate ADI.

If *A* refers to the product being cleaned, active *A1* to the API present in product *A*, and product *B* to the subsequently produced formulation, then the MACO calculation based on ADI values can be expressed as

$$\text{MACO} = (\text{ADI} \times \text{BS} \times \text{SA}) / (\text{MDD} \times \text{ESA})$$

in which ADI is the acceptable daily intake of the active *A1* (%) and is equal to the minimum therapeutic daily dose × safety factor; MDD is the maximum daily dose for product *B* (mg); BS is the batch size of the product *B* (mg); SA is the swab area (cm<sup>2</sup>); and ESA is the equipment surface area shared with product *A* and product *B* (cm<sup>2</sup>).

Table I: Safety factors for the determination of cleaning validation acceptance limits.

Safety factor	Formulation type
10–100	Topical products
100–1000	Oral products
1000–10,000	Injections; eye and ear preparations
10,000–100,000	Research, investigational products

Table I: Safety factors for the determination of cleaning validation acceptance limits.

For the MACO calculation using therapeutic dose unit and safety factor approach, different safety factors have been suggested for various formulation types (see Table I). Nonetheless, a safety factor of 1000 is widely used because it can be thought of as comprising a factor of 10 for adjusting a therapeutically effective dose to a therapeutically noneffective dose, a factor of 10 to accommodate for individual variability in response, and a factor of 10 for making cleaning validation studies robust. The dose-reduction fraction is a measure of the risk involved and is assessed by the manufacturer depending on the actual manufacturing situation.

When it comes to TFs, applying the ADI or therapeutic dose–safety factor approach for MACO calculations is challenging for several reasons, including:

- TFs are not divided into individual dosage units, unlike solid and liquid formulations.
- Dose size per application varies depending upon the total lesion area. Hence, it becomes difficult to establish minimum or maximum daily doses.
- No standardized approach exists for determining dose size. That is, the amount of product recommended to be applied per area of skin per treatment varies from manufacturer to manufacturer.
- The pharmacological effects produced by systemic absorption of the API through oral ingestion are taken into consideration when determining ADI values. In the case of TFs, occasionally enough API is absorbed to cause systemic effects. TFs produce local toxicity even at low doses.

Therefore, a need arises for establishing a rational method to determine cleaning validation acceptance limits for TFs. This article establishes a method for the calculation of MACO for the API of a subsequently manufactured TF by taking into account possible worst cases.

### Worst case I

Assume that active *A1* is marketed in strengths of 2%, 3%, and 5% and that product *B* can be applied on the entire body two to four times per day. The criterion set by Long and Finley can be used to determine the total amount of TF (e.g., cream and ointment) applied on the entire body in one application (6). The criterion describes the dosage of TFs in terms of fingertip units (FTUs). One adult FTU is the amount of ointment or cream expressed from a tube with a standard 5-mm diameter nozzle, applied from the distal crease to the tip of the

index finger. One FTU contains approximately 0.5 g of cream, and it is assumed that approximately 20.25 g (~40.5 FTUs) of cream is needed to cover an adult body. On the basis of these assumptions, the maximum amount of product *B* that can be applied daily would be

$$20.25 \text{ g/application} \times 4 \text{ application/day} = 81 \text{ g/day}$$

To determine the maximum amount of product applied per treatment for other TFs such as medicated shampoos, lotions, toothpaste, and mouthwash, one could consult the European Commission's *Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation* or the manufacturer's in-house criteria (7). For these formulations, the amount of product applied per treatment is fixed; therefore, the maximum amount of product applied per day depends on the maximum number of times the product is used daily.

The lowest available strength of active *A1* in the TF is 2%. This means that approximately 1.62 g (2% of 81 g) of active *A1* if present in 81 g of product *B* will produce its pharmacological effects. Taking into account a safety factor of 1000, active *A1* should not exceed 0.00162 g (1.62 g divided by 1000) in 81 g of product *B*.

Assuming that the batch size for product *B* is 300 kg, MACO of active *A1* to product *B* can be calculated as

$$\text{MACO} = (0.00162 \text{ g} \times 300 \text{ kg} \times 10^6 \text{ mg/kg}) / 81 \text{ g} = 6000 \text{ mg}$$

In other words, MACO of the active *A1* to a batch of product *B* should not be more than 0.1% of the lowest marketed strength–concentration for active *A1*. For the example above, MACO can also be calculated by

$$\text{MACO} = 0.1\% \times 2\% \times 300 \text{ kg} \times 10^6 \text{ mg/kg} = 6000 \text{ mg}$$

From the previous example, it is clear that to calculate MACO of the API in any subsequently manufactured TF, the only information needed is the lowest marketed strength of the API in the TF being cleaned and the batch size of subsequently manufactured finished product. The MACO calculation is independent of minimum and maximum daily dose for product *A* and product *B*, respectively.

MACO in terms of amount of API per surface area of equipment (for swab sampling) can be determined by using the following equation:

$$\text{MACO} = (0.1\% \times C \times \text{BS} \times \text{SA}) / \text{ESA}$$

in which, *C* is the lowest available strength of the API in the product *A* (%), *BS* is the batch size of the product *B* (mg); *SA* is the swab area (cm<sup>2</sup>); *ESA* is the equipment surface area shared by product *A* and product *B* (cm<sup>2</sup>). This equation can be further modified to calculate the residue limits (mg/mL) in the rinse sample by using total volume (*TV*) of rinse or wash solvent portion (mL) and volume (*V*) of rinse sample collected (mL) in place of *ESA* and *SA*, respectively.

## Worst case II

Following the same assumptions and examples described in worst case I, therapeutic doses for TFs may be established in terms of mg/kg body weight/day or mg/cm<sup>2</sup>/day units. According to Long and Finley, 1 FTU covers about 286 cm<sup>2</sup> of skin surface area. This implies that approximately 1.75 mg of the TF is applied per each square centimeter of skin surface area. The dose size for TF may be calculated using the following equation,

$$\text{Daily dose (mg/cm}^2 \text{ /day)} = A \times C \times F$$

in which, *A* is the amount of TF applied in one application per unit area of skin (mg/cm<sup>2</sup>), *C* is the concentration of the API in the TF (%), and *F* is the frequency of application per day (day<sup>-1</sup>).

For calculating minimum daily dose for product *A*, *A* = 1.75 mg/cm<sup>2</sup>, *C* = lowest available strength/concentration of the API in the product *A* = 2%, and *F* = 1 (day<sup>-1</sup>). Therefore, the minimum daily dose for product *A* = 0.04 mg/cm<sup>2</sup>/day, and the maximum daily dose for product *B* = 6.99 mg/cm<sup>2</sup>/day (using *A* = 1.75 mg/cm<sup>2</sup>, *C* = 100%, and *F* = maximum number of times product *B* is applied per day = 4). One point to remember is that the calculation for the maximum daily dose for product *B* is independent of the concentration of API present. Therefore, for a batch size of 300 kg (product *B*) the MACO value may be calculated as

$$\text{MACO} = (\text{minimum daily dose for product } A \times \text{batch size for product } B) / (\text{safety factor} \times \text{maximum daily dose for}$$

product *B*)

$$\text{MACO} = (0.04 \text{ mg/cm}^2 / \text{day} \times 300 \text{ kg} \times 10^6 \text{ mg/kg}) / (1000 \times 6.99 \text{ mg/cm}^2 / \text{day}) = 1500 \text{ mg}$$

Comparing the previous cases, one can observe that the MACO value obtained from the second worst-case scenario is four times less than the value obtained from the first worst case. After thorough analysis of the calculations, however, it can be concluded that the MACO value obtained from worst case II is equal to the MACO value from worst case I divided by the maximum number of applications per day for product *B*. Therefore, if MF is the maximum number of times product *B* that can be applied daily, the MACO value from worst case II can be mathematically expressed as:

$$\text{MACO} = (0.1\% \times C \times \text{BS} \times \text{SA}) / (\text{MF} \times \text{ESA})$$

Therefore, it is the concentration (i.e., percentage) of active *A1* and the number of doses per day for product *B* make a difference when it comes to the calculation of MACO values.

### Criterion based on permitted daily exposure

Another approach for determining MACO uses toxicity data. This strategy is generally used in the industry when dealing with contaminants for which therapeutic doses are not known (e.g., intermediates, precursors, and cleaning agents).

For many drugs, using a safety factor of 0.1% of the lowest recommended therapeutic dose may be reasonable and will produce MACO values at a safe level. This approach cannot be used indiscriminately, however, for several reasons. First, for topical products, the therapeutic doses are not well defined, as discussed previously. A second issue is the mechanism by which toxic effects are produced by the drug. For many drugs, the mechanism by which the toxic effects are produced might be unrelated to the mechanism of pharmacological action. For instance, a drug may cause developmental toxicity (e.g., birth defects) or cancer by a mechanism unrelated to its pharmacological effects. In these cases, using the 0.1% safety factor on the therapeutic dose may still be appropriate but would need to be used with greater caution because the toxic effects may be produced below the safe therapeutic levels.

For these reasons, many manufacturers also include an approach based on toxicity data to calculate MACO values. For many drugs, this approach may be reasonable and has produced MACO values similar to the traditional therapeutic dose/safety factor approach. The basic value of this approach is that a limit can be calculated for cleaning validation purposes based solely on the toxicity of the API present in the TF.

The method uses permitted daily exposure (PDE) values, the criteria commonly used for determining occupational and environmental health hazards. There are two ways to set PDE values. One of the approaches is based on the "no observed effect level/safety factor" (NOEL/SF) approach. In this approach, all of the pertinent animal and human studies are reviewed, and the highest dose that did not cause an effect in the most sensitive health endpoint (the NOEL) is identified. Once a NOEL has been identified, a set of uncertainty (or safety) factors are applied to this value to compensate for limitations in the data and ensure that safe MACO values are obtained. If a NOEL is not available, then a lowest observed effect level (LOEL) can be used. The LOEL value is the lowest dose that causes an effect in the most sensitive health endpoint. A safety factor from 1 to 10 may be considered for extrapolating a LOEL to a NOEL.

The no observed adverse effect level (NOAEL) or lowest observed adverse effect level (LOAEL), are often used interchangeably with the NOEL or LOEL, respectively. For TFs, using NOAEL and LOAEL values is more logical when dealing with local toxic effects caused by the active ingredient.

An equation to determine PDE value for a pharmaceutical can be represented as follows:

$$\text{PDE} = \text{NOEL} \times \text{HBW} \times \text{SF}$$

in which, NOEL is typically in units of milligram of active ingredient administered per kilogram of animal body weight per day (mg/kg-bw/day). NOEL values obtained from human toxicity data and reported in milligrams per day need not to be multiplied by human body weight (HBW), and a safety factor of 0.1 is used to account for the human variability in response. HBW typically is assumed to be 60 kg for an adult male. SF, which is the safety factor for accommodating limitations in the data, is usually 0.01 for converting NOEL to a PDE for topical products.

The second method of calculating PDE is to convert the LD50 value to a NOEL value by applying an empirical

factor. This empirical factor is derived from animal models developed by Layton et al. and can range from 0.0005 to 0.001 (8). The NOEL thus obtained is converted to a PDE value by using the previous equation.

It is important that the NOEL and LD50 values be obtained from dermal toxicity studies. NOEL/LD50 values reported in  $\text{mg}/\text{m}^2/\text{day}$ , the PDE ( $\text{mg}/\text{kg}$ ) can be calculated by using the following equation:

$$\text{PDE (mg/day)} = \text{NOEL (mg/m}^2/\text{day)} \times \text{HSA (m}^2) \times \text{SF}$$

in which, HSA is the average human body surface area, typically assumed to be  $1.62 \text{ m}^2$ .

In addition, a few drugs have NOEL/LD50 values reported in parts per million (ppm), which can be converted to  $\text{mg}/\text{kg}\text{-bw}/\text{day}$  on the basis that 1000 ppm equals  $25 \text{ mg}/\text{kg}\text{-bw}/\text{day}$  for an average 60-kg adult.

MACO( $\text{mg}/\text{swab area}$ ) values based on toxicity data may be calculated as

$$\text{MACO} = (\text{PDE} \times \text{BS} \times \text{SA}) / (\text{MA} \times \text{ESA})$$

in which PDE is the permitted daily exposure for active A1 ( $\text{mg}/\text{day}$ ), BS is the number of fingertip units per batch of final mixture of product B (FTUs), SA is the swab area ( $\text{cm}^2$ ), MA is the maximum number of FTUs of product B applied on the skin per day (FTUs/day) as described under criteria based on the strength of product, and ESA is the equipment surface area shared by product A and product B ( $\text{cm}^2$ ).

For this example, if the PDE value for active A1 =  $0.35 \text{ mg}/\text{day}$ , and assuming BS = 200,000 FTUs, MA = 162 FTUs/day, SA =  $25 \text{ cm}^2$ , and ESA =  $6000 \text{ cm}^2$ , then the MACO ( $\text{mg}/\text{swab area}$ ) value is

$$\text{MACO} = (0.35 \text{ mg/day} \times 200,000 \text{ FTUs} \times 25.0 \text{ cm}^2/\text{swab}) / (162.0 \text{ FTUs/day} \times 6000 \text{ cm}^2) = 1.80 \text{ mg/swab}$$

#### Other criteria

Other criteria typically used in the industry include 10 ppm criterion and visually clean criterion. The former is based on the assumption that not more than 10 ppm of any pharmaceutical ingredient should appear in any other product, and the latter is not an assumption but rather a fixed value of  $0.1 \text{ mg}/25 \text{ cm}^2$  swab area obtained after performing spiking studies. The lowest value obtained from all the MACO calculations based on different criteria is then selected as the acceptance limit for active A1.

#### Conclusion

The determination of MACO for a pharmaceutical agent to the subsequently manufactured product is an inexact science. Each approach has its own set of assumptions and limitations. Any firm that relies on MACO values for their cleaning validation studies must understand the assumptions used in deriving the MACO values. It is the responsibility of pharmaceutical manufacturers and cleaning validation scientists tasked with setting MACO values to estimate a value that is safe for consumers without being so demanding that resources are spent unnecessarily.

**M. Ovais\*** is a pharmaceutical scientist, Xepa-Soul Pattinson (M) Sdn Bhd, 1-5, Cheng Industrial Estate, 75250 Melaka, Malaysia, tel. 006063351515, fax 006063355829, mohammad@xepasp.com  
[<http://mailto:mohammad@xepasp.com>]

**Lai Yeo Lian** is the innovation and development manager at Xepa-Soul Pattinson (M), Laiyl@xepasp.com  
[<http://mailto:Laiyl@xepasp.com>]

\*To whom all correspondence should be addressed.

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**Table I: Safety factors for the determination of cleaning validation acceptance limits.**

Safety factor	Formulation type
10–100	Topical products
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